MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: August 13, 2002

FROM: OTC Analgesic Drug Review Team

TO: Members of Nonprescription Drug Advisory Committee, Consultants and Guests

THROUGH: Division of Over-the-Counter Drug Products
Office of Drug Evaluation V

SUBJECT: September 19 & 20, 2002 NDAC Meeting

The purpose of this memorandum is to provide pertinent background summary information and to identify points to consider as you prepare for the September 19 and 20, 2002 advisory committee meeting. The package you have been provided contains the draft agenda, reviews, and literature that will be addressed during this 2-day meeting. The summary information will be divided by ingredients and days as the issues addressed are may be different.

Day 1 – Acetaminophen Hepatotoxicity, Dosing Duration, and Combination Products

Background:

Acetaminophen, a para-aminophenol (APAP) derivative has been marketed over-the-counter (OTC) since 1960, following NDA approval for an immediate-release 325 mg tablet for the general analgesic indications, dysmenorrhea and fever. On May 15, 1975, McNeil Consumer Products, received NDA approval to market a 500 mg immediate-release capsule formulation of their Extra Strength Tylenol product, with the approved dosing regimen of 1000mg every 4-6 hours, not to exceed 4,000 mg in 24 hours. On July 8, 1977 the recommendations of the Advisory Review Panel provided for the classification of acetaminophen as a Category I analgesic product in the Advanced Notice of Proposed Rule Making for OTC Internal Analgesic, Antipyretic, and Antirheumatic Products. This document permitted the marketing of adult, strength, single-ingredient products in the United States when labeled as follows: 325 mg to 650 mg every 4 hours while symptoms persist not to exceed 3,900 mg in 24 hours and for not more than 10 days of continuous use. In June 1994, the 650-mg extended release caplet and tablet formulation was approved, with a dosage of 2 caplets every 8 hours, not to exceed 3,900 mg in 24 hours.

The data assessed by the Panel in 1977 to determine efficacy and safety of acetaminophen included animal toxicity data, clinical trial data, and published literature case reports. Based on the LD50 calculations obtained from animal toxicity data, the LD50 in humans was estimated to be 400 mg/kg/day, a level 5 to 7 times the maximum recommended dose of 3,900 mg in humans weighing between 50 and 70 kg. Moreover, the Panel considered at that time, that APAP-associated hepatotoxicity in humans might be exacerbated by glutathione depletion. Based on this information, the Panel recommended the inclusion of the following liver warning for APAP products: "Do not exceed recommended dosage because severe liver damage may occur." For chronic use, the Panel recommended the warning "Do not exceed recommended dosage or take for more than 10 days, because severe liver damage may occur". In addition, the Panel also recommended additional studies to determine if other warnings were needed for these products to be used safely.

The Panel also considered data on the metabolism of acetaminophen in the presence of various types of liver disease, including alcoholic liver cirrhosis. The Panel found that the evidence suggested that the overall elimination of acetaminophen by conjugation is decreased in alcohol abusers. They suggested that this decreased conjugation and the observed susceptibility of chronic alcohol abusers to hepatotoxicity of acetaminophen was not necessarily due to liver disease but resulted from the induction of micorsomal enzymes by the chronic use of alcohol. However, the Panel did not recommend a warning concerning the use of acetaminophen by individuals with a history of liver disease or chronic alcohol abuse.

The publication of the Internal Analgesic, Antipyretic, and Antirheumatic tentative final monograph (TFM) in 1988 allowed for the additional dose of acetaminophen (500 mg) to be marketed OTC. In addition, to providing for this dose, the document also addressed comment, both pros and cons, relating to the inclusion of a hepatic warning on the labels of these products. Many comments opposed the liver warning recommendations. The comments included statements that: 1) there was insufficient data, 2) this would discourage consumers from ever using the product, 3) this would encourage suicidal persons to misuse APAP products, 4) there was a lack of documented cases in children specific to the children's products. Other comments that endorsed the warning cited increasing usage of the products in both adults and children who had a right to know that fatalities and liver damage had been reported with overdoses. After considering all of the available data, the agency concluded that insufficient information was presented to support the Panel recommended warnings and that they should not be adopted at that time. Additional information was requested with regard to cumulative dosing, dosing duration, and underlying conditions that might exacerbate hepatotoxicity prior to initiating a specific warning. (Refer to Section I of the Packet, which contains relevant portions of the Panel Report, and of the TFM.) The agency also concluded that there was insufficient data to support a warning on the increased risk of liver toxicity when acetaminophen is taken with substances or drugs that induce microsomal enzyme activity, i.e., alcohol, barbiturates, or prescription drugs for seizures.

In response to the TFM, the agency received numerous comments and new data concerning the need for an alcohol warning for acetaminophen. On June 29, 1993, the agency's Nonprescription Drug Advisory Committee (NDAC) met to consider the need for a warning. NDAC concluded that an alcohol warning should be required for acetaminophen but that the warning should not be implemented until it had a chance to consider data on the risk of alcohol with other OTC analgesics. NDAC further recommended that any warning should include organ-specific information. In a subsequent meeting (September 8, 1993), NDAC concluded that an alcohol warning should also be required for OTC NSAIDs. However, the committee was unable to agree on whether the warning should also include organ-specific information. In the Federal Register of November 14, 1997, the agency proposed an alcohol warning for acetaminophen and the other OTC NSAIDs that included organ specific information. For acetaminophen, the organ specific warning was for liver; whereas for the OTC NSAIDs the warning was for GI bleeding. The requirement for an alcohol warning for OTC analgesic drug products was finalized on October 23, 1998.

Efficacy:

The material contained within this package does not specifically address efficacy. The efficacy of these products was reviewed prior to either the Panel's determination that acetaminophen was a Category I analgesic ingredient.

Safety:

There is substantial marketing experience with acetaminophen in both the prescription (in combination products) and the over-the-counter use. The data provided will focus on hepatotoxicity from unintentional overdoses (either as a result of taking too much in an attempt to relieve an acute symptom or taking multiple products containing the same active ingredient). This information has been obtained from the FDA's SRS and AERs databases, published literature, poison control databases, foreign data, and summarized safety presented at the time of NDA and monograph review.

Points to Consider:

When reviewing the briefing package consideration should be given to identifying the factors that may contribute to an increased risk for developing unintentional APAP associated hepatotoxicity. Once these factors are identified, the committee will be asked to provide specific recommendations on the labeling and/or marketing of products containing acetaminophen that will decrease the risk of developing unintentional overdose. Alternatively the committee may recommend additional research be conducted to address specific issues. This research may attempt to develop solutions to identify factors, which contribute to increased risk, or to determine whether a factor represents an increased risk.

Day 2 - Aspirin (ASA) and OTC Nonsteroidal Anti-inflammatory Drugs (NSAIDs) – Gastrointestinal (GI) Bleeding and Renal Toxicity

Background:

Aspirin has been widely available since its discovery in the late 1800s. In 1977, the Advisory Panel recommended the continued OTC availability of aspirin and its derivatives for up to 4 g/day in divided doses. Doses exceeding 4 gm/day for OTC use may directly correlate with increasing toxicity, ranging from tinnitis to gastrointestinal bleeding. The 1988 Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use; Tentative Final Monograph proposed aspirin as Category I.

In 1985, ibuprofen became the first NSAID marketed for OTC use. Ibuprofen was approved as a 200-mg tablet that could be taken at doses of 1-2 tablets every 4-6 hours, not to exceed 1200 mg in 24 hours. During the early advisory committee deliberations the issue of warning statements for OTC use and specific warning concerns, i.e., GI bleeds and renal toxicity were addressed. Since that approval, two additional NSAIDs were approved for OTC marketing, naproxen sodium and ketoprofen. With each advisory committee meeting the issue of GI bleeds, hepatotoxicity and renal toxicity were addressed. The data provided at these meetings was not considered compelling that organ-specific warnings would need to be required on the consumer labeling for OTC doses of these products, since only limited data were available to suggest that these were significant findings for OTC doses

The adverse event profile of both aspirin and NSAIDs are well known, with the majority of the literature addressing NSAID toxicity at the prescription dose. Both of these drug classes commonly have effects on the gastrointestinal, hepatic and renal systems. The ingestion of salicylates and NSAIDs may result in epigastric distress, nausea, and vomiting. Further, they may also cause gastric ulceration, exacerbation of peptic ulcer symptoms, gastrointestinal hemorrhage, and erosive gastritis. The frequency of occurrence in higher and prescription doses has been described as 1-2%. However, reports have been described at lower doses for both.

Salicylates and NSAIDs can also produce hepatic and renal effects, which are usually reversible for the products and at OTC ASA and NSAID doses. Salicylates can produce at least two difference forms of hepatic injury. In one form, hepatotoxicity is dose-related and usually occurs in individuals with underlying connective tissue diseased, and is characterized by elevated hepatocellular enzymes. Resolution occurs with cessation of salicylate. The other form occurs in association with Reye's syndrome. The hepatocellur toxicity that occurs with NSAIDs is characterized by transaminase elevations, which is reversible once the NSAID is stopped. NSAIDs and aspirin may also decrease creatinine clearance and increase creatinine concentrations particularly in individuals with underlying hypovolemia, impaired renal function, or decrease renal blood flow. These findings may revert to normal when the offending NSAID or aspirin product is discontinued. However, cases of occasional dialysis and use of corticosteroids have been needed until function is recovered. Further, all of these products may result in salt and fluid retention with resultant elevations of blood pressure.

Efficacy issues for each specific product will not be addressed.

Safety:

There is substantial marketing experience with both aspirin and NSAIDs. The data that will be presented today will address the literature and FDA databases and foreign marketing experience.

Points to Consider:

The toxicity that occurs with the use of NSAIDs and ASA are different than acetaminophen; however, the global issues remain similar. When reviewing the briefing package consideration should be given to identifying the factors that may contribute to an increased risk for developing unintentional gastrointestinal bleeding and renal tonicities associated with ASA or NSAID use. The discussion on this day will focus on identifying the risks associated with the use of these products and then deciding whether certain measures should be taken that could decrease the risk of occurrence or decrease the morbidity should an adverse event occur. There are several options that can come out of this section of the meeting. These options would include: 1) no modification of labeling is needed; 2) addition of an organ-specific warning for the carton; 3) consumer information leaflet to describe in more detail potential adverse events; 4) consumer educational campaign(s); and 5) the need for additional research.